Symptomatic Hepatocellular Liver Injury With Hyperbilirubinemia in Two Patients Treated With Rivaroxaban

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IMPORTANCE Treatment with the new oral anticoagulant rivaroxaban can be associated with severe liver injury.

OBSERVATIONS We report 2 patients with predominantly hepatocellular liver injury that had onset during treatment with rivaroxaban. Both were symptomatic, had massively elevated transaminase activity levels and hyperbilirubinemia, and fulfilled the criteria of Hy's law. Liver biopsy in 1 patient revealed centroacinar hepatocyte necrosis as the predominant finding. Both patients showed a rapid biochemical and clinical recovery after discontinuing rivaroxaban therapy. Between 2008 and 2013, 42 cases of liver injury possibly associated with rivaroxaban treatment have been reported to the Swiss Agency of Therapeutic Products (Swissmedic). Thirteen of these patients fulfilled the criteria of Hy's law.

CONCLUSIONS AND RELEVANCE Treatment with rivaroxaban can be associated with severe, symptomatic liver injury. Physicians should be aware of this adverse drug reaction. We propose rapid discontinuation of treatment with rivaroxaban in case of symptomatic liver injury and, taking into account its severity, avoiding reexposure.

Rivaroxaban is a selective, competitive, active site-directed factor Xa inhibitor\textsuperscript{1} that is currently approved in many countries for the prevention of systemic embolism in patients with nonvalvular atrial fibrillation, prevention of deep vein thrombosis after orthopedic surgery, and for the treatment of deep vein thrombosis and/or pulmonary embolism.\textsuperscript{2} In some countries, rivaroxaban has also been approved for the prevention of atherothrombotic events in patients with acute coronary syndrome. Based on predictable pharmacokinetics and pharmacodynamics, a fixed dose of rivaroxaban is usually administered once daily without routine coagulation testing. Approximately one-third of the orally administered drug is eliminated unchanged by the kidney, and the rest is metabolized in the liver and eliminated via bile or urine.\textsuperscript{2,3} Hepatic metabolism of rivaroxaban is mainly by cytochrome P450 (CYP) 3A4, facilitating interactions with CYP3A4 inhibitors or CYP inducers.\textsuperscript{2,3}

The most common adverse effects of rivaroxaban use are hemorrhages observed mostly in the gastrointestinal tract, whereas cerebral or spinal hemorrhages are rarer.\textsuperscript{4,5} Other adverse effects include mainly skin reactions and liver injury. In an analysis of the 4 RECORD (Regulation of Coagulation in Major Orthopedic Surgery Reducing the Risk of Deep Venous Thrombosis and Pulmonary Embolism) studies including patients who had undergone orthopedic surgery, 2.33% of the 6183 patients treated with rivaroxaban had transaminase levels more than 3 times the upper limit of normal (ULN).\textsuperscript{6} Symptomatic liver injury has recently been reported in a series of 14 patients treated with rivaroxaban.\textsuperscript{7} We report 2 additional patients treated with rivaroxaban with symptomatic liver injury who fulfilled the criteria of Hy's law.\textsuperscript{8}

Report of Cases
The first patient was a 52-year-old man who developed liver injury 2 months after starting therapy with rivaroxaban (Table). Rivaroxaban (10 mg per day) was used for the prevention of deep vein thrombosis after internal fixation of a tibia fracture. Two months after starting treatment with rivaroxaban, the patient presented with loss of appetite, nausea, and jaundice. Viral hepatitis was excluded serologically, the patient had no history of alcohol or drug abuse, and hemodynamic liver injury was excluded by a Doppler ultrasound that had normal results. Analysis of a blood sample revealed a massive elevation of serum alanine aminotransferase concentration (1740 U/L [ULN, 59 U/L; to convert to microkatal per liter, multiply by 0.0167]) and a slight elevation of alkaline phosphatase concentration (136 U/L [ULN, 129 U/L; to convert to microkatal per liter, multiply by 0.0167]) (Figure 1 and Table), compat-
ible with hepatocellular liver injury.9 As expected from the clinical presentation, the serum bilirubin concentration was elevated (18.7 mg/dL [ULN, 1.5 mg/dL]; to convert to micro-
moles per liter, multiply by 17.104). All drug treatment (pan-
toprazole sodium, dipyrone, ibuprofen lysine, and rivaroxa-
baban) was discontinued on the first day of hospitalization.
During hospitalization, a liver biopsy was obtained, which re-
vealed severe lobular hepatitis with perivenular confluent nec-
rosis (Figure 2) and no other pathological features. The lobu-
lar architecture was preserved, and fibrosis of portal tracts was
not present. These histological findings were judged to be well
compatible with drug-related liver injury. Signs and symp-
toms of liver injury reversed rapidly after cessation of rivar-
oxaban treatment; the patient had a full clinical and partial bio-
chemical recovery after 14 days. The patient was not reexposed
to rivaroxaban or the other drugs with which he had been
treated. Taking into account the fact that the patient had been
treated with other potentially hepatotoxic drugs (see Discus-
sion), the causality assessment was “possible.”10

The second patient was a 73-year-old woman who had re-
ceived a total knee replacement and was treated with rivar-
oxaban (10 mg per day) for the prevention of deep vein throm-
bosis. Four weeks after starting rivaroxaban treatment, she
developed jaundice and pruritus and required hospitaliza-
tion (Table). The diagnostic tests revealed mixed liver injury
(aspartate aminotransferase level, 139 U/L [ULN, 34 U/L; to con-
vert to microkatals per liter, multiply by 0.0167]; alanine ami-
notransferase level, 334 U/L [ULN, 41 U/L]; gamma-glutamyl
transpeptidase level, 566 U/L [ULN, 40 U/L; to convert to mi-
crokatals per liter, multiply by 0.0167]; alkaline phosphatase
level, 363 U/L [ULN, 104 U/L])9 and hyperbilirubinemia (se-
rum bilirubin concentration, 7.54 mg/dL [ULN, 1.1 mg/dL]).
Rivaroxaban therapy was discontinued on the day of hospi-
talization, whereas treatment with levothyroxine sodium and
lisinopril was continued. Viral hepatitis was excluded sero-
logically, screening for autoimmune liver disease had nega-
tive results, a Doppler ultrasound of the liver had normal re-
results, and the patient had no history of alcohol or drug abuse.
A liver biopsy was not obtained in this patient. Liver enzyme

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
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<tbody>
<tr>
<td>Age, y/sex</td>
<td>52/M</td>
<td>73/F</td>
</tr>
</tbody>
</table>
| Latency time from exposure to developm
ent of liver injury, mo             | 2         | 1         |
| Concomitant drugs                  | Pan
toprazole, ibuprofen, dipyrone | Lisinopril, lev
othyroxine |
| Symptoms                           | Nausea, reduced appetite, ja
undice | Nausea, reduced appetite, pr
ritis, jaundice |
| Liver enzymes and serum biliru
bin, maximal value, ×ULN             |           |           |
| Alanine aminotransferase            | >29       | >8        |
| Alkaline phosphatase                | 2         | >3        |
| Bilirubin                           | >12       | >7        |
| Factor V                           | Normal    | Unknown   |
| Viral hepatitis                     | Negative  | Negative  |
| Epstein-Barr virus                  | Negative  | Unknown   |
| Cytomegalovirus                     | Negative  | Unknown   |
| Autoimmune hepatitis                | Unknown   | Negative  |
| Liver sonography                    | Normal    | Normal    |
| Liver biopsy performed              | Yes       | No        |
| Recovery after discontinuation of rivaroxaban treatm
ent                         | Full clini
cal recovery 2 wk after discontinuing all drug treatment | Full clinical and biochemi
cal recovery 2 wk after discontinui
ng rivaroxaban treatment |
| Rechallenge                         | No        | No        |
| Causality assessment                | Possible  | Probable  |

Abbreviation: ULN, upper limit of normal.
levels and bilirubin concentration resolved completely within 2 weeks after rivaroxaban treatment had been withdrawn. The patient was not reexposed to rivaroxaban. The causality assessment in this patient was “probable.”

Discussion

Drug-induced liver injury (DILI) is one of the most common drug-related adverse reactions and can result in acute liver failure, which may necessitate emergency liver transplantation or end fatally. The diagnosis of DILI is challenging because the liver histological analysis may not be diagnostic, specific biomarkers are lacking, and there are multiple additional factors such as treatment with other drugs or concomitant liver diseases that can produce similar clinical, laboratory, and/or histological features.

The assessment of suspected DILI cases consists therefore of 2 major diagnostic processes: the exclusion of other causes of liver injury and the identification of a pattern of disease manifestations that is temporally related to exposure to the suspected drug. In the present cases, other diseases such as viral hepatitis, exposure to alcohol or other toxins, autoimmune hepatitis, and hemodynamic liver injury have been excluded and there were no direct (case 1) or indirect markers of liver cirrhosis. The clinical pattern of liver injury was quite similar in the 2 patients: both experienced nausea and loss of appetite, were jaundiced, and showed a rapid improvement after rivaroxaban therapy was discontinued. Massive elevations of serum transaminase activities and bilirubin concentrations were the predominant laboratory findings, whereas alkaline phosphatase level was elevated only slightly. The results of the liver biopsy in patient 1, showing perivenular hepatocyte necrosis as the key finding, were compatible with the predominant hepatocellular pattern of the clinical presentation.

Besides clinical pattern and liver biopsy findings, the rapid clinical and biochemical response after discontinuation of rivaroxaban treatment is also compatible with drug-associated liver injury. Both patients had already started to improve 1 day after discontinuing rivaroxaban treatment and eventually recovered over the next 2 weeks. Because rivaroxaban has a half-life in the range of 10 hours, a rapid improvement of liver injury could be expected on the assumption that the toxic effects are related to the presence of rivaroxaban or a metabolite with a short half-life.

The causality rating was “possible” for case 1 and “probable” for case 2. In case 1, also ibuprofen and, less likely, pantoprazole could have caused liver injury, whereas liver injury has so far not been reported for dipyrone. In case 2, only treatment with rivaroxaban but not the other drugs (levothroidine and lisinopril) was discontinued. Taking into account the similarity of the clinical presentation of the 2 patients, we consider treatment with rivaroxaban the most likely cause of liver injury in both patients.

The present report is not suited to provide a mechanism for the hepatotoxicity of rivaroxaban. Because immunological features were absent in the liver biopsy of patient 1, as well as in the clinical presentation of both patients, metabolic toxic effects of rivaroxaban and/or of a rivaroxaban metabolite are a more likely possibility. The perivenular localization of liver damage is compatible with the formation of toxic metabolites because CYP3A4, the most important CYP for rivaroxaban metabolism, has a centroacinar localization in adults.
Between 2008 and 2013, 42 cases of suspected adverse drug reactions (including the 2 cases described herein) of the organ class “liver and biliary system disorders” (according to the World Health Organization’s adverse reaction terminology) associated with rivaroxaban have been submitted to the Pharmacovigilance Unit of the Swiss Agency of Therapeutic Products (Swissmedic). The reporting rate of liver injury associated with rivaroxaban in Switzerland increased during the past 2 years, probably primarily reflecting increased prescription rates. Per reported case, a mean of 2.6 suspected drugs (median [range], 1 [1-11]) and a mean of 1.4 liver events were coded, including jaundice in 14 and liver failure in 1 of them. Thirteen cases (our 2 cases included) showed a pattern of liver injury similar to that of the 2 cases described by us with alanine aminotransferase level greater than 3 times ULN and serum bilirubin concentration greater than 2 times ULN, fulfilling the principles of Hy’s law.8

One of the 6 Swiss Regional Pharmacovigilance Centers recently published a series of 14 cases of rivaroxaban-induced DILI reported to that center (included in the 42 Swiss reports).7 Similar to our 2 cases, 10 of the 14 patients had alanine aminotransferase values greater than 5 times ULN; 9, serum bilirubin concentrations greater than 2 times ULN; most of them were symptomatic; and 13 patients recovered after discontinuing rivaroxaban treatment. The similarity in the clinical presentation of the patients reported by us and by Russmann et al7 strengthens the conclusion that rivaroxaban was causing liver injury in these patients.

### Conclusions

Treatment with rivaroxaban can be associated with severe hepatocellular liver injury, with some patients fulfilling the criteria of Hy’s law. After discontinuation of rivaroxaban therapy, affected patients show a rapid clinical and biochemical improvement, eventually resulting in complete recovery. Physicians should be aware of this potentially severe adverse drug reaction and should inform patients about possible symptoms when prescribing the drug. We propose rapid discontinuation of treatment with rivaroxaban in case of symptomatic liver injury and, considering the possible severity of liver injury, avoiding reexposure. A warning about symptomatic liver injury should be included in the drug labels.

### REFERENCES